B

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,711	10/27/2003	Gary S. Stein	07917-164001 / UMMC 02-25	7812

26161 7590 04/07/2006

FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 04/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/694,711	STEIN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *1-29,36 and 41-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-35 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/05, 3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 03/15/06 has been acknowledged.

Claims 30-35 and 37-40 are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Election/Restrictions

Applicant's election without traverse of Group VI, claims 30-35 and 37-40 in the reply filed on 10/13/05 is acknowledged.

Claims 1-29, 36 and 40-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/13/05.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 30-31 are rejected under 35 U.S.C. 102(a) as being by Strausberg Genebank AN: BC017234, 2001. The scope of invention as claimed encompasses a nucleic acid molecule comprising the sequence ggcattggtctgattcacc (SEQ ID NO:10). The cited art teaches a nucleotide sequence that comprises ggcattggtctgattcacc (see attached comparision). Thus the cited art clearly anticipate the invention as claimed.

SEQ ID NO:10	1	GGCATTGGTCTGATTCACC	19
AN: BC017234	1472	GGCATTGGTCTGATTCACC	1454

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 32-35 and 37-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of invention as claimed encompasses any antisense nucleic acid molecle, any siRNA molecule, any composition or any agent that inhibits the expression of HiNF-P. Besides the antisense sequence of SEQ ID NO:17, the specification as field fails to disclose any other antisense nucleic acid molecule, siRNA molecule, composition or agent that is capable of inhibiting cell proliferation via inhibition of expression or activity of HiNF-P expression. Similarly, the specification fails to describe the second composition that s sufficient to inhibit NPAT expression or activity.

Applicant is referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see http://www.uspto.gov). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. Since the specification fails to disclose fails to disclose any antisense nucleic acid molecule (other

than SEQ ID NO:17), siRNA molecule, composition or agent that is capable of inhibiting cell proliferation via inhibition of expression or activity of HiNF-P expression; or a second composition that inhibits NPAT expression or activity; it is not possible to envision the claimed composition. One cannot describe what one has not conceived. (See Fiddes v. Baird, 30 USP2d 1481 at 1483). Therefore, the lack of disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Furthermore the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).* For example, in the instant case the antisense nucleic acid sequences or siRNA as claimed has been defined only by a statement of function that broadly encompasses a nucleic acid molecule that inhibits the expression of HiNF-P or NPAT, which conveyed no distinguishing information about the identity of the claimed genetic material, such as its relevant structural or physical characteristics. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of even a single member of this

genus would not be representative of other nucleic acid constructs genus and is insufficient to support the claim.

Claims 30-35 and 37-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Since the specification as field fails to disclose any other antisense nucleic acid molecule (besides SEQ ID NO:17), any siRNA molecule, any composition or agent that is capable of inhibiting cell proliferation via inhibition of expression or activity of HiNF-P expression and a second composition (as claimed) that is sufficient to inhibit NPAT expression or activity; it is unclear how one skilled in the art use the invention as claimed (supra). In addition the specification fails to disclose that the nucleic acid sequence of SEQ ID NO:10 is capable of inhibiting the HiNF-P expression or activity in any cell (in-vitro or in vivo). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise (infra). The applicant's disclosure does not enable one skilled in the art to practice the invention as claimed without further undue amount of experimentation, which requires the identification and characterization of any and all agents that inhibits HiNF-P or NPAT expression or acitivity. At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970).

Claims 30-35 and 37-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature Of Invention

The instant invention relates to method of decreasing cell proliferation by administering to the cell a composition or agent that inhibits Histone Nuclear Factor P (HinF-P) expression or activity.

Breadth Of Claims And Guidance Provided in the Specification

The scope of invention as claimed encompasses a method of decreasing cell proliferation in-vivo on in-vitro by administering to the cell any composition or agent that inhibits Histone Nuclear Factor P (HinF-P) expression or activity. At best the specification teaches that the isolated SAOS2 cells **(in-vitro)** treated with the HiNF-P antisense oligonucleotide (SEQ ID NO:17) that was directed against a segment in the 3' end of the HiNF-P mRNA exhibited a greater than 90% reduction in HiNF-P mRNA and protein levels. The specification further asserts that the reduction of cells in S phase in samples treated with antisense oligonucleotide (average value 36%) relative to control cells (average value 42%) was consistently observed in all experiments. The specification further asserted that antisense-induced reduction in HiNF-P levels thus resulted in a quantitatively statistically significant 10-15% reduction in the fraction of cells progressing through S phase. The specification concluded that these data show that inhibiting HiNF-P expression (e.g., by introducing antisense oligonucleotides into a cell) is an effective method of reducing cellular proliferation.

Besides the antisense sequence of SEQ ID NO:17, the specification as field fails to disclose any other antisense nucleic acid molecule, siRNA molecule, composition or agent that is capable of inhibiting cell proliferation via inhibition of expression or activity of HiNF-P expression. In addition the specification fails to disclose that the nucleic acid sequence of SEQ ID NO:10 is capable of inhibiting the HiNF-P expression or activity in any cell (in-vitro or in vivo). In addition, besides the decreasing the proliferation of

isolated cells (in-vitro) using the antisense sequence of SEQ ID NO:17, the speciation as filed fails to provide any evidence that administration of antisense sequence of SEQ ID NO:17 or any other agent (as claimed) via any and all routes of administration (oral, nasal, ocular, dermal or systemic etc) is capable of inhibiting proliferation of cells or treating a disease characterized by excessive proliferation (i.e. any cancer).

State Of Art And Predictability

There are many problems long recognized in nucleic acid based therapies, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. The problems of nucleic acid based therapies are well known in the art. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, 6:72-81, 2000,) and Jen et al. (Stem Cells 18:307-319, 2000). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects.

Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery.... presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in any type of cell, with a resultant therapeutic outcome, as claimed. The specification provides examples wherein antisense is delivered to cultured cells, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of antisense to any other type of cell, including mammalian cells. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in*

vivo (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies") states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of antisense nucleic acids into any type of cell, either *in vivo* or *in vitro*, by the broadly disclosed methodologies of the instant invention, would result in successful attenuation/inhibition of a target gene. One of skill in the art would not know how to deliver antisense nucleic acids to an organism in such a way that would ensure an amount sufficient to attenuate expression of a target gene is delivered to the proper cell.

In fact, the state of the art is such that successful delivery of nucleotide sequences to a target cell *in vivo* or *in vitro*, such that the oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of inhibiting gene expression using nucleic acids *in vivo* are unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate cell/organ, at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, attenuating or inhibiting expression of a target gene such that the organism exhibits a loss of function phenotype.

The specification does not provide the guidance required to overcome the art-recognized unpredictability associated with the therapeutic use of antisense oligonucleotides. The field of antisense-based therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods. In order to practice the claimed invention *in vivo* a number of variables would

have to be optimized, including 1). the mode of delivery of the oligonucleotide to an organism that would allow it to reach the targeted cell, 2). the amount of oligonucleotide that would need to be delivered in order to allow inhibition of the expression of a target gene once it reached the proper cell and 3). ensuring the oligonucleotide remains viable in a cell for a period of time that allows inhibition of the gene to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each antisense nucleic acid. At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970).

Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broad claims drawn to the therapeutic use of antisense oligonucleotides, since the state of the prior art teaches that the therapeutic use of antisense oligonucleotides is neither routine nor predictable. The disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). Thus, one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 30-35 and 37-40 are not enabled.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If

attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL
PRIMARY EXAMINER
ART UNIT 1633